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**14. ABSTRACT**

The objective of the research was to evaluate the hemostatic efficacy of patch and granule formulations of CP-305 in normal and coagulopathic swine models. The studies were carried out using the lethal groin injury and liver laceration models. Application of the dressings to the aforementioned injuries resulted in a 70 to 90% survival rate after 180 minutes compared to 100% mortality using a standard battlefield dressing. Hemostasis was achieved using only the dressing and 5 minutes of manual compression. The dressings were stable allowing for resuscitation of the swine to basal cardiovascular parameters. The thermal stability of the active ingredient was evaluated from 2 to 40 degrees Centigrade. Preliminary research was carried out to elucidate the mechanism(s) of action of CP-305.

**15. SUBJECT TERMS**
hemostatic, dressing, swine, groin injury, liver injury



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FINAL TECHNICAL REPORT

GRANT #: N00014-05-C-0269

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INSTITUTION: University of Tennessee Health Science Center

GRANT TITLE: Development of Hemostatic Agents

AWARD PERIOD: 1 October 2005 - 30 June 2007

OBJECTIVES: To translate investigational hemostatic agents developed in the rat model to swine models of lethal groin injury and liver laceration. This objective evaluated the efficacy of patch and granule formulations of capsaicin (CP-305) in normal and coagulopathic swine models. The thermal stability of the drug patches was studied at elevated temperatures to assess shelf life of the hemostatic agent. The remaining objectives were to study the mechanism of action of vanilloid compounds on whole blood aggregation and develop bio-degradable vanilloid compounds.

APPROACH: The efficacy of vanilloid compounds as hemostatic agents was first demonstrated in the rat model of lethal groin injury under grant number N00014-04-1-0756. The translation of the technology to a model relevant to human hemorrhage was employed to assess the efficacy of the patch and granule formulations of CP-305. Therefore, Yorkshire X Landrace swine weighing 40-50 kg were instrumented under deep anesthesia to monitor mean arterial pressure (MAP), heart rate (HR), continuous cardiac output (CCO), mixed venous oxygen saturation ($SVO_2$). In the coagulopathic model core and rectal temperature was monitored via a Swan-Ganz catheter and rectal probe; respectively. Swine were either maintained at 37 to 39°C or cooled to 31 to 32°C for the coagulopathic studies.

Complex groin injuries were created by complete division of the femoral artery and vein approximately 3cm below the inguinal ligament. Shed blood was be evacuated from the wound at the vascular injury site until the MAP dropped to 35 mm Hg. Hemostatic patches, granules, or standard field dressing (SD) were applied to the vascular injury site and held in place for 5 minutes using manual compression. Pressure was released and a hold phase of 30 minutes was started, no external bandage, elastic band, or pressure cuff was utilized after the release of manual pressure. Resuscitation was initiated after a 30 minute interval to reestablish basal MAP using 500ml of 6% Hetastarch in 0.9% saline followed by 0.9% saline, as needed, to re-establish basal MAP. The primary endpoints were survival 180 minutes post resuscitation, continued hemorrhage or re-bleeding after dressing application and early mortality (defined as an MAP below 25 mmHg or apnea for a period of 5 minutes).

Liver injury was accomplished by an 8cm long, 1cm deep incision in the thick section between the left and right medial lobes in the region of the branches of the left and right distal hepatic arteries and veins. After injury induction, the blood was continuously suctioned from the peritoneal cavity; the hemostatic agents were applied into the wound 30 seconds post-injury and manual pressure applied for 5 minutes. Pressure was released and when required, resuscitation with 6% Hetastarch in 0.9% saline was initiated after compression to maintain the MAP within 10% of the baseline values. The primary

endpoints were survival 180 minutes post resuscitation, re-bleeding after dressing application and early mortality (defined as an MAP below 25 mmHg or apnea for a period of 5 minutes).

The mechanism(s) of hemostatic action of CP-305 were evaluated using whole blood aggregation measurements and biochemical markers of aggregation stimuli. A synthetic route for producing hydrolysable esters of CP-305 was developed.

ACCOMPLISHMENTS: The efficacy of the CP-305 loaded patch and granule hemostatic compositions, relative to placebo compositions, was demonstrated in the swine models of lethal groin injury and liver laceration. The compositions were compared to the hemostatic efficacy of a SD in the normothermic groin injury model.

Patch evaluation in the lethal groin injury model.

*Normothermic model*: The swine model of groin injury, using 5 male and 5 female animals (n = 10 per dressing), was carried out in normothermic animals to assess hemostatic patch efficacy. The lyophilized patches consisted of a drug loaded plasticized chitosan backing underneath a collagen coated CP-305 layer. The studies evaluated placebo (0% drug), 5%, and 10% drug percent loaded patches and the SD dressing. Patches were applied to the vascular injury site in combination with four 4 by 4 gauze squares (4 ply of gauze per square). Manual pressure was applied to the hemostat for 5 minutes then released, in instances where patches dislodged due to adhesion of coagulated blood to gloves; the patches are reseated using 1 additional minute of pressure. No further intervention in the form of continued pressure, elastic bandages, or pressure cuff was utilized to stabilize the vascular injury site. In the SD studies, the dressing was folded and manually compressed to form a V shape and applied to the injury site. This step was taken to help the SD to conform to the shape of the groin wound. The 30 minute hold phase was followed by resuscitation with 500ml of 6% Hetastarch in 0.9% saline followed by 0.9% saline, not exceeding a total volume greater than 5 volumes of shed blood, at a flow rate of 999 ml/60 min.

Transection of the femoral bundle resulted in a mean blood loss of 773 ml compared to a mean blood loss of 1126 ml in the SD studies (Table 1).

**Table 1**

| Experimental Group | Number of animals | Body Weight (kg) | Hemorrhage Volume (ml) | Percent Hemorrhage* | Resuscitation Volume (ml) |
|---|---|---|---|---|---|
| Placebo patch | 10 | 49.3 ±1.1 | 813±58 | 25.3 | 635±44 |
| 5% patch | 10 | 49.0±1.0 | 712±95 | 22.4 | 644±40 |
| 10% patch | 10 | 49.8±1.8 | 793±88 | 24.5 | 680±87 |
| SD | 10 | 47.9±1.8 | 1126±133# | 36.1 | 300±84 |

* Estimated total blood volume was calculated based on 65ml/kg

# Statistically significant ($p < 0.001$) greater blood loss relative to all patch formulations.

The studies utilizing the SD dressing resulted in 100% mortality within 100 minutes. Within these studies 50% of the animals survived the 30 minute hold phase; however, increased vascular pressure associated with resuscitation forced the SD dressing out of the injury site resulting in exsanguination (Figure 1, Panel A).

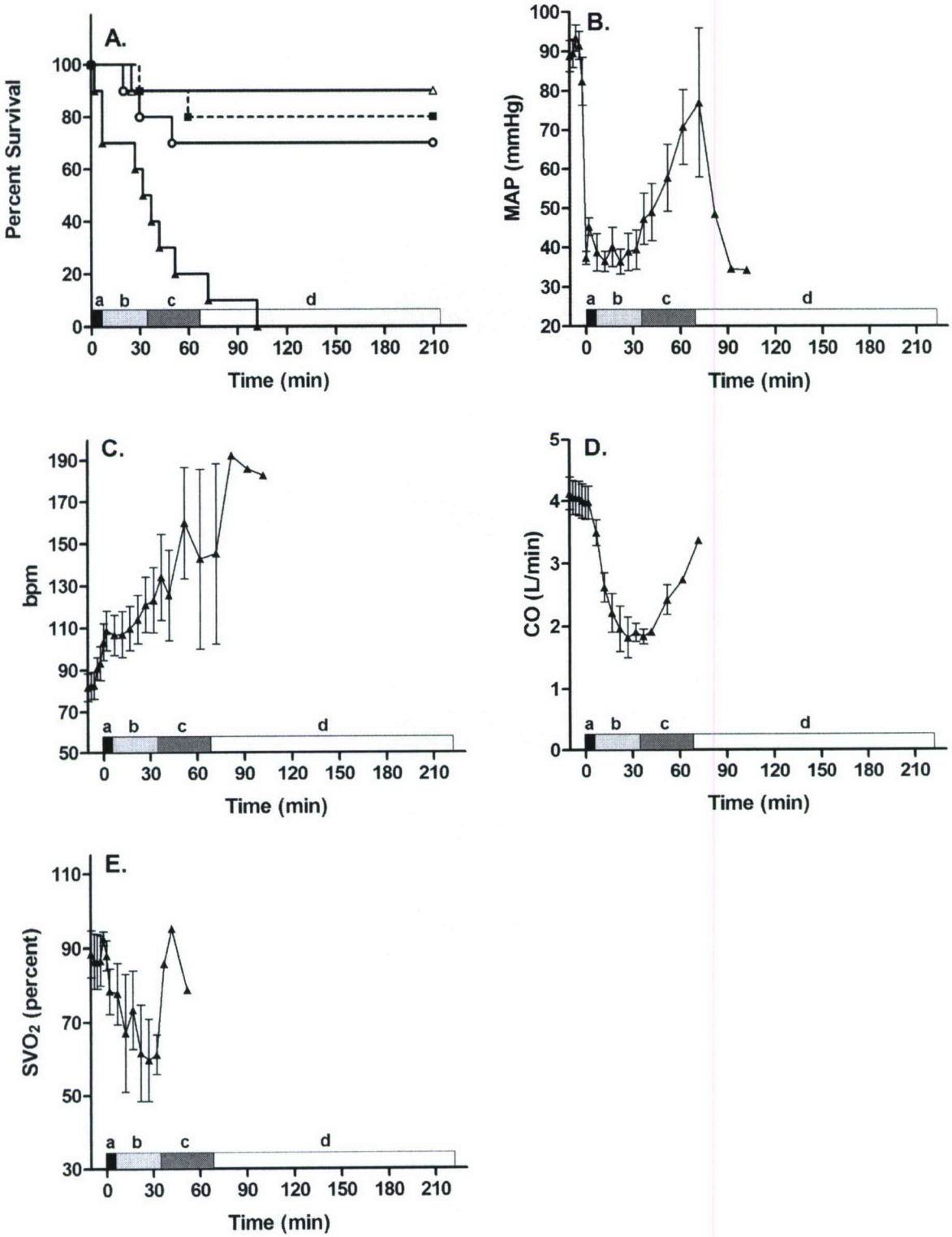



**Figure 1**. Experimental results of the SD dressing study showing the percent survival (Panel A), MAP (Panel B), heart rate (Panel C), cardiac output (Panel D), and mixed venous oxygen (Panel E). The treatments are identified by SD dressing (▲), placebo patch (■), 5% patches (○), and the 10% patch as (Δ). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the 30 minute hold phase, (c) is the resuscitation phase, and (d) is the 180 minute observation phase.

In the absence of external fixation, the SD dressing was progressively pushed out of the injury site as a function of increased MAP associated with resuscitation. However, it is believed that application of an elastic bandage as described by Alam (Alam HB et al. J. Trauma, 2003, 54, 1077-82; Alam HB et al. J. Trauma, 2004, 56, 974-83) would have manifested a 50% survival rate, consistent with Alam, thus indicating we have reproduced Alam's complex groin injury model. Our decision not to utilize standard battlefield procedures reflected an effort to validate the hemostatic efficacy of CP-305 dressing in the absence of added hemostasis measures.

The CP-305 patches formulations utilized in the swine studies were a modification those developed for rat studies. The original formulation was brittle and disintegrated in the vascular injury site; therefore, a modified chitosan patch employing a proprietary plasticizer matrix was developed. While the new formulations imparted flexibility and wound conforming properties it negatively impacted the release of CP-305 from the matrix. To overcome the slow release of CP-305 from the patch, a film of CP-305 blended in collagen (selected based on pro-coagulation effects) was added to the surface of the patch. The film in the final lyophilized product rapidly dissolved and released CP-305.

The reformulated placebo, 5% drug, and 10% drug loaded patches were evaluated in the complex groin injury model. The 10% patches achieved a 90% survival rate compared to 80% for the placeboes and 70% for 5% patches. Two mortalities occurred during the resuscitation phase due to rupture of the wound seal, one each for placebo and 5% patches. All patch formulations exhibited a high seal rate; the differences in the survival populations between the placebo, 5%, and 10% patches were statistically insignificant as determined by a logrank test. Analysis of the survival populations of the placebo, 5%, and 10% patches relative to the SD dressing were highly significant with $p$ values of 0.0002, 0.002, and <0.0001, respectively (Figure 3, Panel A). In addition, the mortality within treatment groups did not manifest a bias based on sex.

Hemostasis of the injury site was one measure of the efficacy of the dressing, the second criteria was resuscitation to affect an increase in cardiovascular parameters to basal values. The principle marker of the resuscitation endpoint was the reestablishment of the MAP to basal level, a parameter that was found to decrease as a function of time under spontaneous breathing anesthesia (Figure 2). Based on these findings, the resuscitation protocol using 500ml of 6% Hetastarch in 0.9% saline followed by 0.9% saline, as required, was successful in restoring the basal MAP without hemostasis failure at the vascular injury site (Figure 3, Panel C). In general, the reperfusion interval occurred within a 30 minute interval requiring only 500ml of Hetastarch; however, supplemental saline administration increased the mean reperfusion time 44±8 minutes. The secondary cardiovascular parameters HR, CCO, and $SVO_2$ manifested a return to stable base line values in all experiments where re-bleeding did not occur.

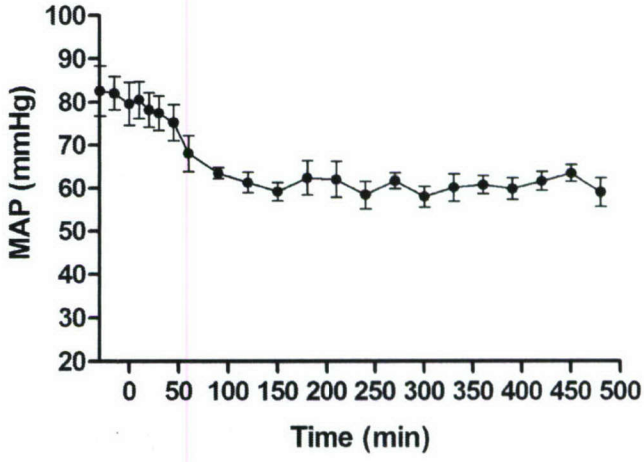



**Figure 2.** In hemorrhagic shock studies, using identical animals with respect to weight, strain, and instrumentation (n = 6), the effect of isofluorane anesthesia on the MAP was evaluated in spontaneously breathing animals. A decline in MAP was manifested over 100 minutes after which time the MAP reached a plateau around 65 mmHg.

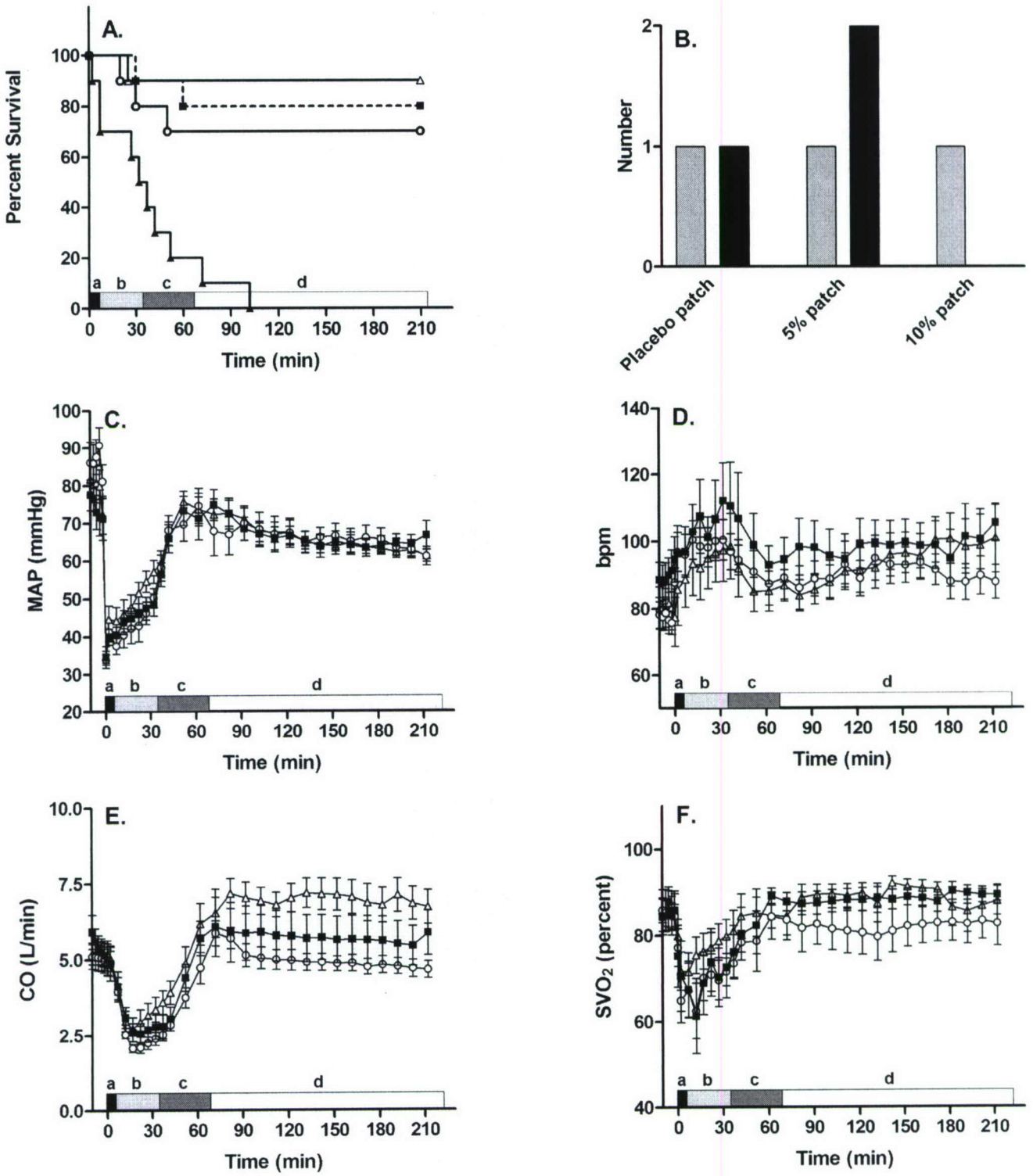



**Figure 3**. Experimental results of the placebo, 5%, and 10% patch dressings showing the percent survival (Panel A), mortality based on sex (Panel B, gray females and males black), MAP (Panel C), heart rate (Panel D), cardiac output (Panel E), and mixed venous oxygen (Panel F). The treatments are identified by SD dressing (▲), placebo patch (■), 5% patches (○), and the 10% patch as (△). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the 30 minute hold phase, (c) is the resuscitation phase, and (d) is the 180 minute observation phase.

Based on survival percentages and cardiovascular parameters there were statistical differences between the placebo and drug loaded patches. However, a qualitative difference in the vascular injury site seal of the placebo versus 5% and 10% loaded patches was evident (Figure 4). In the absence of CP-305, leakages around the patch and into the wound cavity lead to significant clot formation thus stabilizing the dressing-wound seal. These observations may reflect the prothrombotic collagen effects; however, it does not appear that collagen provides a statistically significant effect considering the reported 71% survival rate of HemCon (chitosan based dressing) dressing (Alam, HB.et al. J. Trauma, 2004, 56, 974-83). This interpretation must be viewed cautiously because our model did not employ external fixation of the dressing.

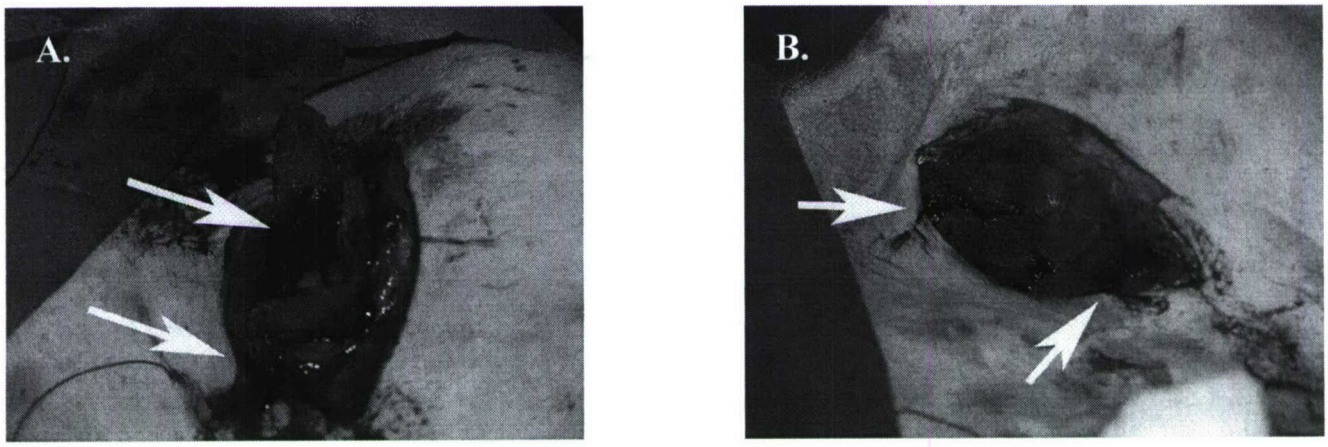



**Figure 4**. Representative pictures of the placebo patch (Panel A) and a drug loaded patch (Panel B) in the vascular injury site after the 180 minute observation phase. The white arrows in Panel A show areas of extensive blood clotting in and around the wound site; additionally, the placebo dressing manifest reduced adhesion to the tissue in the wound site. In comparison, the drug loaded patches provide tight seals in the wound bed with limited or no seepage of blood around the dressing (white arrows Panel B).

*Hypothermic model*: Coagulopathy is a complicating condition which negatively impacts intervention in server hemorrhage. The majors underlying factors that contribute to coagulopathy are hemodilution and hypothermia. Due to the importance of coagulopathy in hemostatic dressing evaluation, the patch formulations were tested under coagulopathic conditions induced by hypothermia. Hypothermic animals with and average core temperature of 32° C were subjected to the groin injury model (Figure 5, Panel E). These conditions caused a reduction in hemorrhage rate, but it did not affect the overall experimental parameters (Table 2). The SD dressings were not evaluated under hypothermic conditions due to the 100% mortality in normothermic animals. Hypothermia was not predicted to improve the SD outcomes thus justifying our efforts to reduce animal numbers.

**Table 2**

| Experimental Group | Number of animals | Body Weight (kg) | Hemorrhage Volume (ml) | Percent Hemorrhage* | Resuscitation Volume (ml) |
|---|---|---|---|---|---|
| Placebo patch | 10 | 50.9 ±1.0 | 855±107 | 25.8 | 657±54 |
| 5% patch | 10 | 46.8±1.1 | 786±71 | 25.8 | 605±42 |
| 10% patch | 10 | 47.7±0.7 | 615±53# | 19.8 | 664±57 |

* Estimated total blood volume was calculated based on 65ml/kg

# Statistically significant ($p < 0.001$) less blood loss relative to placebo formulation.

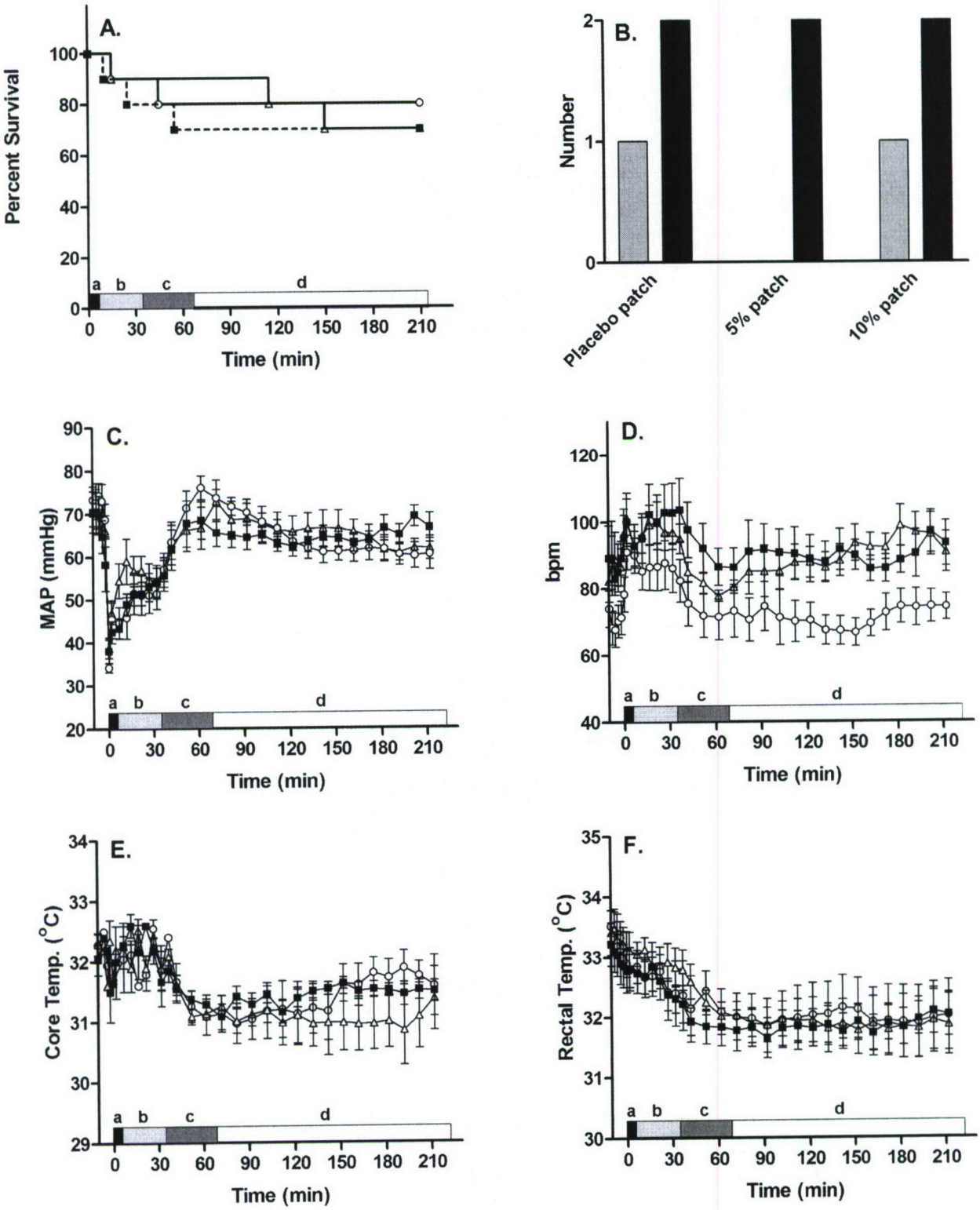



**Figure 5**. Experimental results of the placebo, 5%, and 10% patch dressings showing the percent survival (Panel A), mortality based on sex (Panel B, gray females and males black), MAP (Panel C), heart rate (Panel D), core temperature (Panel E), and rectal temperature (Panel F). The treatments are identified by placebo patch (■), 5% patch (○), and the 10% patch as (△). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the 30 minute hold phase, (c) is the resuscitation phase, and (d) is the 180 minute observation phase.

Application of the 5% patches resulted in an 80% survival rate compared to 70% for the placebo and 10% patches. Two mortalities occurred during the resuscitation phase due to rupture of the wound seal, one each for placebo and 10% patches. The survival profiles of the hypothermic studies were statistically indistinguishable from the normothermic studies; furthermore, no treatment showed a statistically significant improvement between groups. Additionally, the integrity of the seals was closely matched between treatment groups within the hypothermic, paralleling the qualitative results in the normothermic studies (Figure 4).

Hypothermia was accomplished utilizing a re-circulating refrigerator unit in combination with ice packs on the neck. The cooling process required approximately 60 minutes during which time the MAP decreased by an average of 15mmHg. The decline is most likely associated with time under anesthesia and not an effect of hypothermia. Notwithstanding, qualitative observations indicate that hemorrhage rates following vascular injury were slower than those observed in the normothermic animals. It is not believed that reduce hemorrhage rates affected experimental outcomes since the target hemorrhage MAP of 35mmHg was reached and resuscitation to basal MAP was achieved. The resuscitation phase utilized Hetastarch or saline at 32°C in an effort not to alter the core temperature; however, fluid additions caused a decrease in the core and rectal temperatures by approximately one degree (Figure 5, Panels E and F). The decline in core temperature correlates with 2 mortalities during reperfusion; however, but it is not likely that increased coagulopathy is responsible.

The application of the placebo, 5%, and 10% CP-305 dressing to the complex groin injury resulted in 70 to 90 percent survival. A critical point that can only be addressed qualitatively, by inspection of seal quality, is efficacy of CP-305 in promoting hemostasis. The decision to utilize collagen as a release matrix does not allow the separation of hemostatic effects. However, the studies of the granular formulations of CP-305 support the hemostatic properties of CP-305.

Granule evaluation in the lethal groin injury model.

The granular formulations were developed on the hypothesis that significantly increased surface area of the granules precluded the need for a rapidly dissolving carrier (collagen) of CP-305. By coating CP-305 on the surface and adsorbing it into the granules significantly high concentrations of the drug would be achieved in the wound bed. Therefore, a proprietary granule formulation of chitosan was pan coated with CP-305 and tested (20 grams/animals) in the complex groin injury previously described.

*Normothermic model*: The hemorrhage volumes of the 5% granules were statistically lower as compared to the placebo (Table 3) and all formulations were significantly lower than SD the dressing.

**Table 3**

| Experimental Group | Number of animals | Body Weight (kg) | Hemorrhage Volume (ml) | Percent Hemorrhage* | Resuscitation Volume (ml) |
|---|---|---|---|---|---|
| Placebo granules | 10 | 46.3 ±1.2 | 810±34 | 26.9 | 457±43 |
| 5% granules | 10 | 46.6±0.7 | 595±46# | 19.6 | 500±33 |
| 10% granules | 10 | 47.6±1.1 | 770±97 | 24.8 | 443±56 |
| SD | 10 | 47.9±1.8 | 1126±133 | 36.1 | 300±84 |

* Estimated total blood volume was calculated based on 65ml/kg

# Statistically significant ($p < 0.001$) less blood loss relative to the placebo formulation.

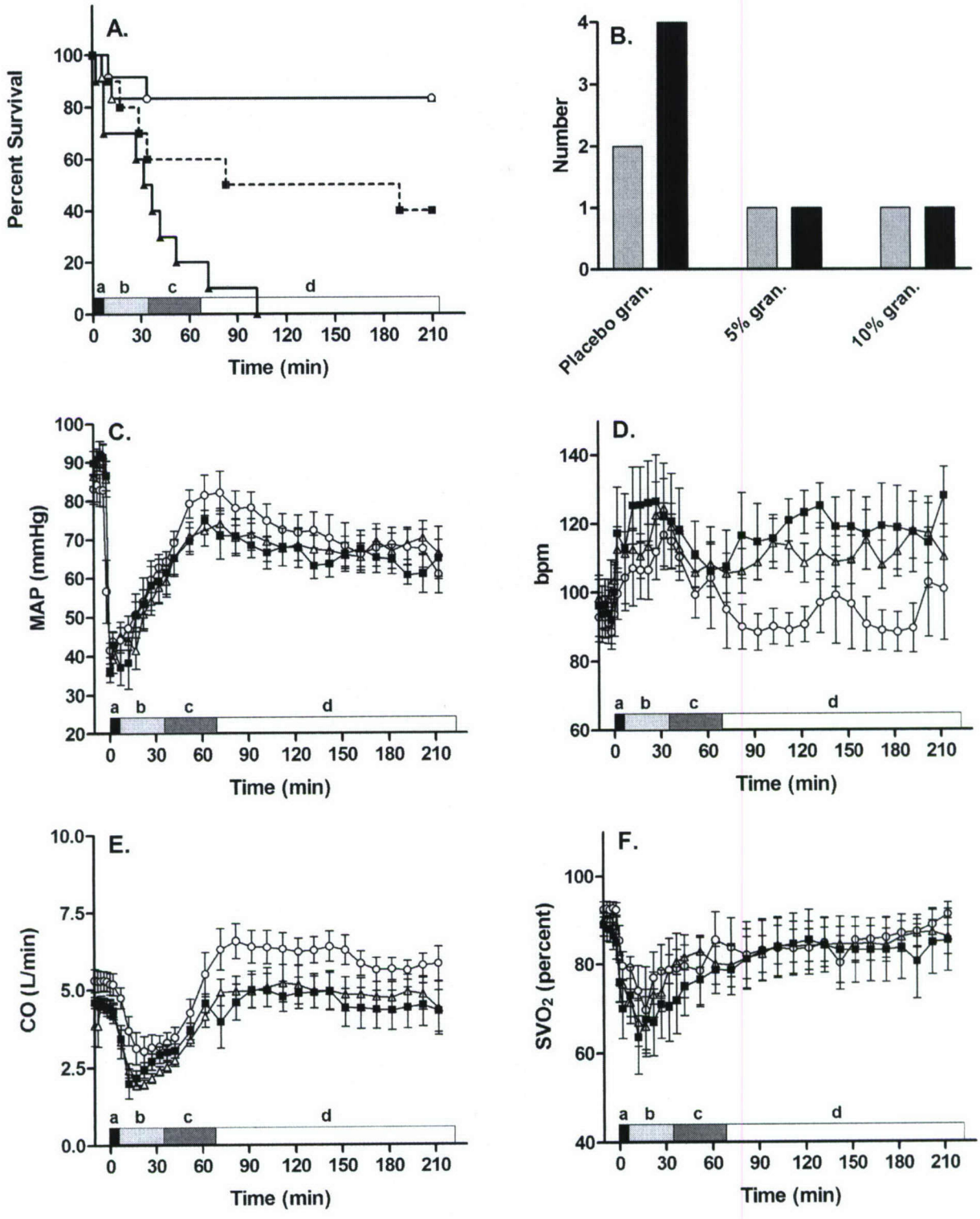



**Figure 6**. Experimental results of the placebo, 5%, and 10% granule dressings showing the percent survival (Panel A), mortality based on sex (Panel B, gray females and males black), MAP (Panel C), heart rate (Panel D), cardiac output (Panel E), and mixed venous oxygen (Panel F). The treatments are identified by SD dressing (▲), placebo granules (■), 5% granules (○), and the 10% granules as (Δ). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the 30 minute hold phase, (c) is the resuscitation phase, and (d) is the 180 minute observation phase.

The placebo granules, in contrast to the placebo patches, were ineffective hemostatic agents, manifesting a 60% mortality rate (Figure 6, Panel A). This outcome in combination with the survival rate in the drug loaded granules supports a hemostatic effect of CP-305. Specifically, the 5% and 10% CP-305 loaded granules experiments manifested an 80% survival rate. The difference in survival between the placebo and 5% granules was statistically significant ($p = 0.045$) and whereas the 10% granules was not ($p = 0.063$) using a 95 percent confidence level. In the experiments shed blood was suctioned until the end of the 30 minute hold phase then discontinued. The statistically significant increase in hemorrhage volume in placebo studies (Table 3) also supports the efficacy of CP-305 in hemorrhage control. Analysis of the survival populations of the placebo, 5%, and 10% granules relative to the SD dressing were highly significant with $p$ values of 0.022, <0.0001, and <0.0001, respectively (Figure 3, Panel A). The mortality within treatment groups did not manifest a statistically significant difference based on sex.

The principle marker of the resuscitation endpoint, the return to basal MAP, was achieved in 80% of the 5 and 10% granules with no re-bleeding during the resuscitation phase (Figure 6, Panel C). The secondary cardiovascular parameters HR, CCO, and $SVO_2$ manifested a return to stable base line values in all experiments. It is noteworthy the HR is significantly depressed in the 5% granules relative to the placebo and 10% treatments. Decreased HR was also seen in the 5% patch hypothermic studies. The origin of the depressed HR is unknown since the response is not consistent throughout the 5% formulations.

The granular formulations did not exhibit a qualitative difference in the seal quality as did the patch formulations. In general, the granules sealed without leakage or re-bleed or failed to seal and exsanguination resulted. In our opinion the granular formulations containing CP-305 provide superior hemostasis to that of the patch formulations in normothermic animals. The granules conform to the wound bed, are less technically demanding to apply, and when "set" form a hard wound adherent material.

*Hypothermic model*: The granule dressings were evaluated in coagulopathic animals using the model previously described. The hemorrhage volumes of the 5% and 10% granules were statistically lower as compared to the placebo (Table 4).

**Table 4**

| Experimental Group | Number of animals | Body Weight (kg) | Hemorrhage Volume (ml) | Percent Hemorrhage* | Resuscitation Volume (ml) |
|---|---|---|---|---|---|
| Placebo granules | 10 | 48.1 ±0.8 | 813±130 | 26.0 | 467±33 |
| 5% granules | 10 | 46.4±1.3 | 605±136# | 20.1 | 500±0 |
| 10% granules | 10 | 47.5±0.9 | 650±92# | 21.1 | 467±24 |

* Estimated total blood volume was calculated based on 65ml/kg

# Statistically significant ($p < 0.001$) less blood loss relative to the placebo formulation.

In coagulopathic animals, the placebo granules did not provide a statistically significant increase in survival relative to the placebo patch, 50 versus 70% respectively. Analysis of the placebo granules versus the 5 and 10% drug load granules fail to meet statistical significance using a 95 percent confidence level ($p = 0.121$ and 0.058, respectively, Figure 7, Panel A).

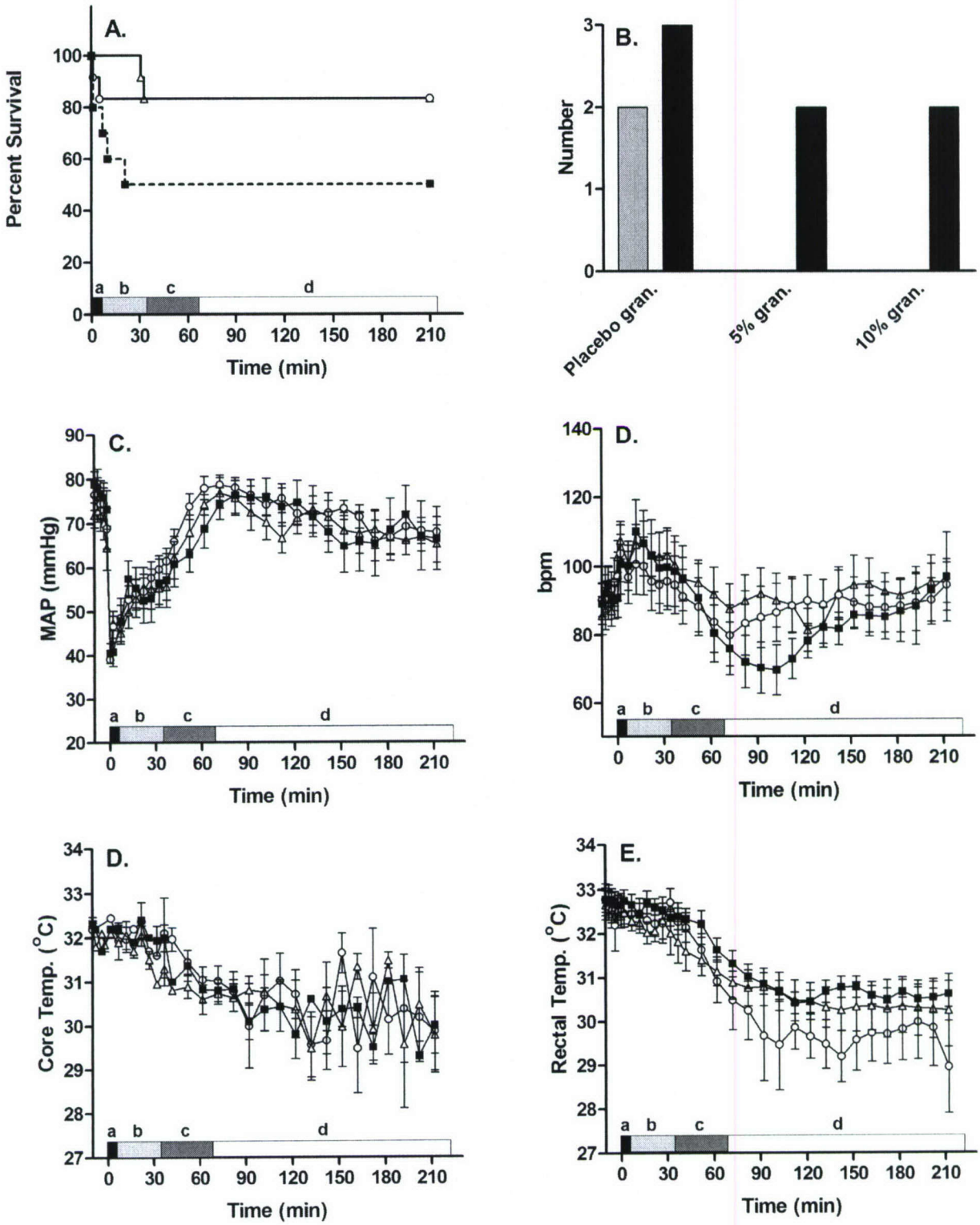



**Figure 7**. Experimental results of the placebo, 5%, and 10% granule dressings showing the percent survival (Panel A), mortality based on sex (Panel B, gray females and males black), MAP (Panel C), heart rate (Panel D), core temperature (Panel E), and rectal temperature (Panel F). The treatments are identified by placebo granules (■), 5% granules (○), and the 10% granules as (Δ). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the 30 minute hold phase, (c) is the resuscitation phase, and (d) is the 180 minute observation phase.

In these studies re-bleeding occurred prior to the resuscitation phase, intact seals were stable to the increase of the MAP to basal levels. The seal integrity was indistinguishable with the integrity observed in the normothermic studies. The conclusion from the complex groin injury model is that the granular formulation is an efficacious hemostatic dressing that is quick and easy to administer. The data collected on the effectiveness of CP-305 in hemostasis supports continued research to optimize the granule based dressings.

Patch evaluation in the liver injury model.

The efficacy of a hemostatic dressing can vastly differ depending on the animal model. Dressings are typically evaluated for efficacy under mixed arterial and venous bleeding (groin injury model), arterial bleeding (arteriotomy model) and venous bleeding conditions (Grade V liver injury model). The efficacy of our CP-305 based patch and granule dressing has been demonstrated in the mixed arterial and venous bleeding. In an effort to assess to scope of hemostatic indications of these dressing, hemostatic experiments were conducted using a liver injury model.

Liver injury was accomplished by an 8cm long, 1cm deep incision in the thick section between the left and right medial lobes (Figure 8). After injury induction, the blood was continuously suctioned from the peritoneal cavity; the hemostatic agents were applied into the wound 30 seconds post-injury and manual pressure applied for 5 minutes. Pressure was released and when required, resuscitation with 6% Hetastarch in 0.9% saline was initiated after compression to maintain the MAP within 10% of the baseline values. The primary endpoints were survival 180 minutes post resuscitation, continued hemorrhage after dressing application and early mortality.

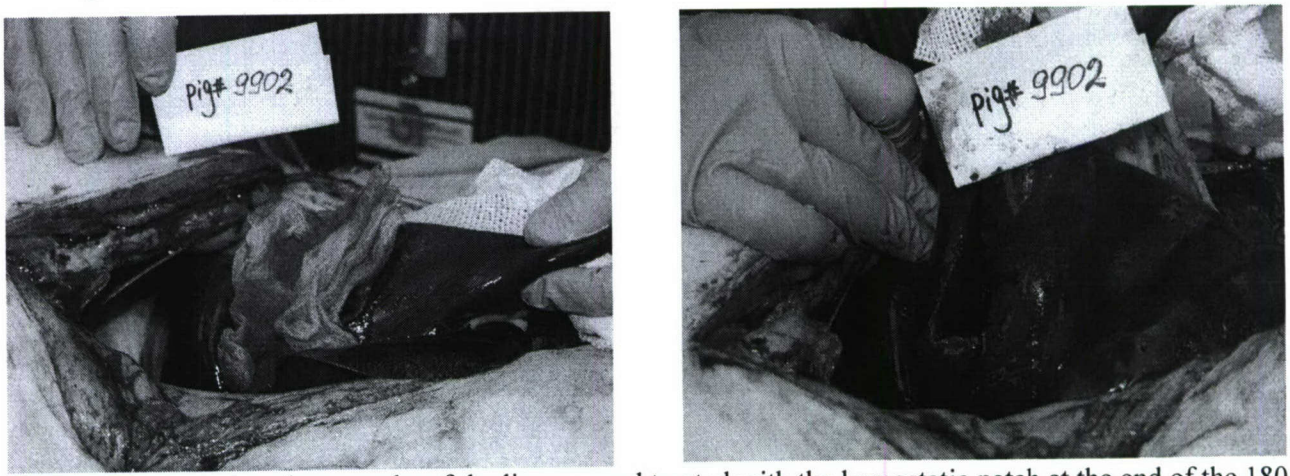



**Figure 8.** Representative photographs of the liver wound treated with the hemostatic patch at the end of the 180 minute hold phase (Panel A) and the wound after dressing removal (Panel B).

**Table 4**

| Experimental Group | Number of animals | Body Weight (kg) | Hemorrhage Volume (ml) | Percent Hemorrhage* | Resuscitation Volume (ml) |
|---|---|---|---|---|---|
| Placebo patch | 10 | 48.3 ±1.0 | 244±31 | 7.8 | 500 |
| 5% patch | 10 | 50.7±1.9 | 360±108# | 10.9 | 450±104 |
| 10% patch | 10 | 49.3±0.6 | 172±18 | 5.4 | 250±76 |

* Estimated total blood volume was calculated based on 65ml/kg

# Statistically significant ($p < 0.001$) greater blood loss relative to the placebo and 10% formulation.

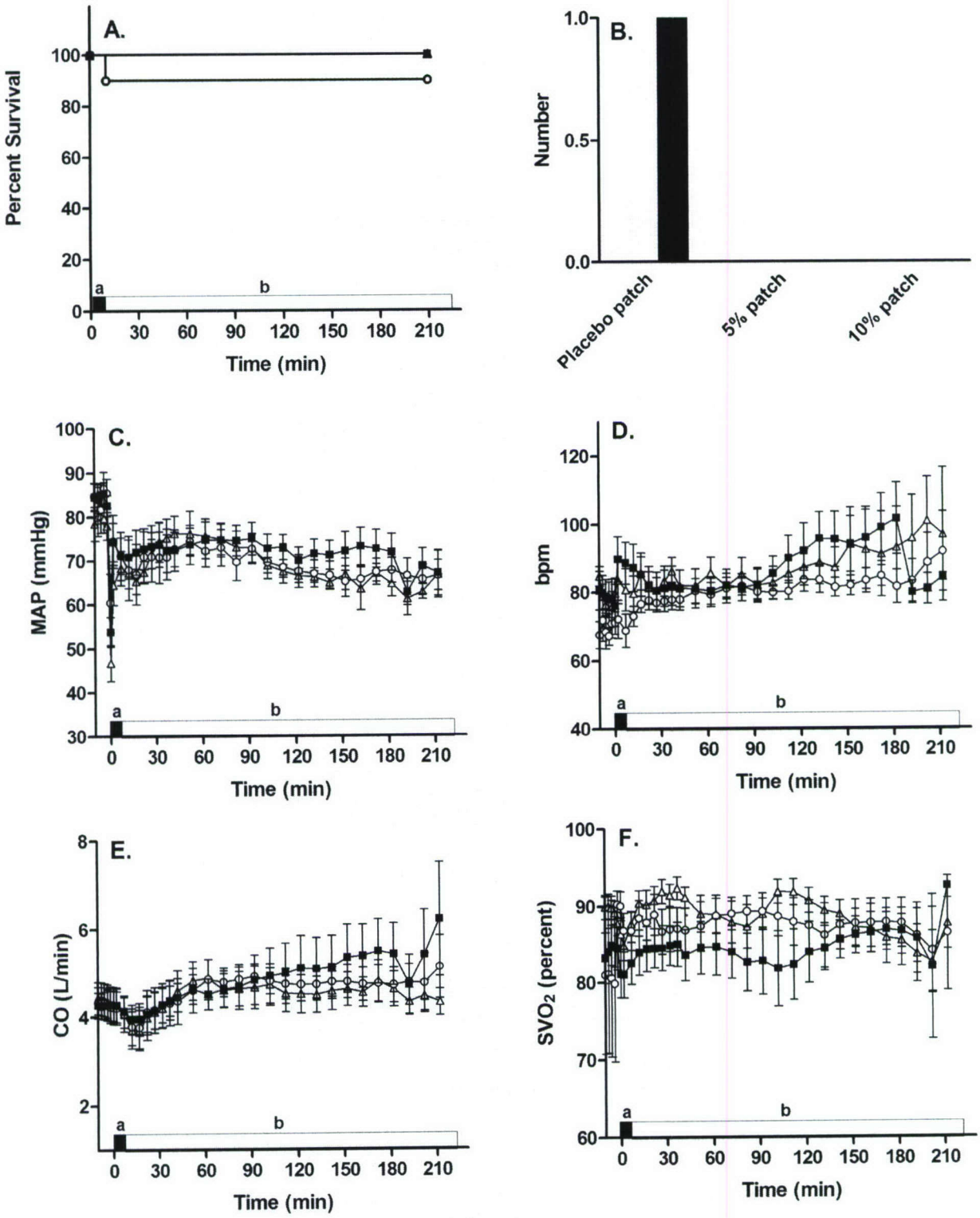



**Figure 9**. Experimental results of the placebo, 5%, and 10% patch dressings showing the percent survival (Panel A), mortality based on sex (Panel B, gray females and males black), MAP (Panel C), heart rate (Panel D), core temperature (Panel E), and rectal temperature (Panel F). The treatments are identified by placebo patches (■), 5% patches (○), and the 10% patches as (△). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the observation/resuscitation phase.

The liver injury model used for these studies was a different from the standardized Grade V liver injury model previously reported (Holcomb, JB et al. J. Trauma, 1999, 46, 49-57, Pusateri, AE.et al. J. Trauma, 2003, 55, 518-26). The incision method did not produce large stellate wounds; however, the incision did result in a mean decrease in MAP of 28% within 30 seconds. This decrease in MAP within 30 seconds of the incision meet the criteria set forth by Holcomb for a Grade V injury, *i.e.* "10% decrease in MAP within 30 seconds after injury virtually ensured a grade V injury". Thus we believe that we have reproduced a high flow low pressure venous injury. In this model hemorrhage was controlled after application and manual compression with little or no post application bleeding. Interestingly, there was a statistically significant increase in hemorrhage with the 5% patch compared to placebo and 10% patches (Table 4) resulting from post application hemorrhage in 2 animals. In general, the modest hemorrhage limited fluid replacement to maintain the MAP. The specific number of animals resuscitated was 2 for the placebo, 3 for the 5%, and 5 animals for the 10% patches.

The patches proved highly effective in stopping hemorrhage from the liver laceration, exhibiting a 90-100% seal rate (Figure 9, Panel A). In all but two instances the patches formed complete seals that did not leak over the course of the experiment. The injury and subsequent hemorrhage represented a average 8 percent blood loss thus the MAP, HR, CO, and $SVO_2$ (Figure 9, Panels C thru F) recovered via normal compensatory mechanisms. The seal quality of the placebo patches in the liver injury studies did not qualitatively differ from the drug loaded patches, as was observed in the groin injury model. However, it can not be concluded that collagen is the determining factor in hemostasis since there is no statistical significance between the placebo patches and granules (no collagen) in the liver injury model (see below).

Granule evaluation in the liver injury model.

In the granular dressing studies, liver injury produced a mean decrease in the MAP of 37% within 30 seconds (Figure 10, Panel C). The total blood loss between experimental groups was statistically insignificant (Table 5). Compensatory mechanisms reduced the number of animals resuscitated to 2, one each for the placebo and 10 percent dressing. Thus normal cardiovascular parameters were reestablished within 30 minutes of the laceration (Figure 10, Panels C thru F).

**Table 5**

| Experimental Group | Number of animals | Body Weight (kg) | Hemorrhage Volume (ml) | Percent Hemorrhage* | Resuscitation Volume (ml) |
|---|---|---|---|---|---|
| Placebo granules | 10 | 49.5 ±1.0 | 311±67 | 9.7 | 500 |
| 5% granules | 10 | 50.7±1.6 | 244±40 | 7.4 | 0 |
| 10% granules | 10 | 49.4±0.9 | 282±57 | 8.8 | 500 |

* Estimated total blood volume was calculated based on 65ml/kg

The survival of the animals treated with the 5% and 10% granules was 100%; this was also the case for the placebo dressing until 160 minutes of observation when 2 seals failed (Figure 10, Panel A). The granular formulations provided a distinct advantage over the patch dressings being less demanding to apply to the laceration. The patch dressings required manual alignment into the wound area whereas the granules flowed into and conformed to the wound bed providing rapid hemostasis.

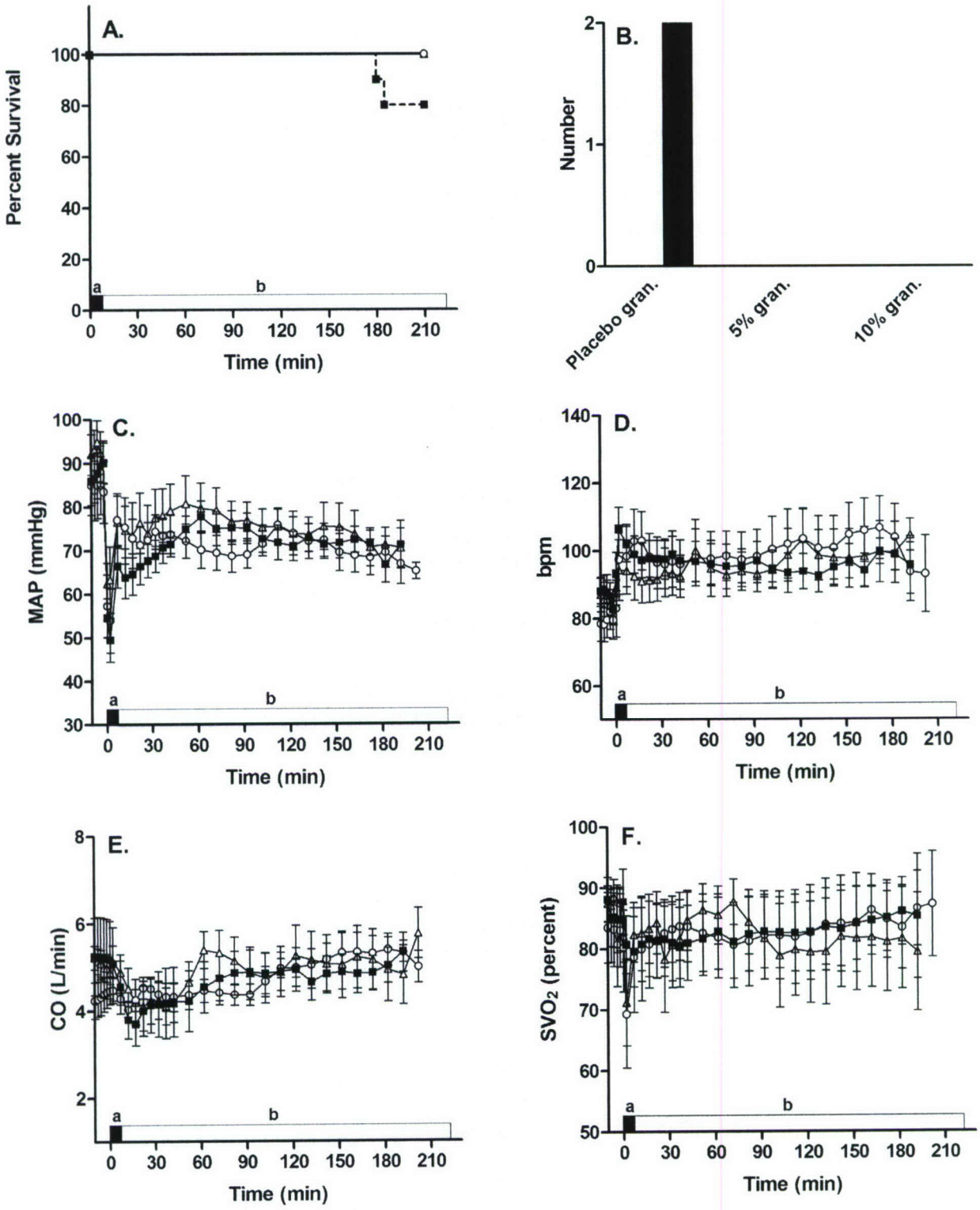



**Figure 10**. Experimental results of the placebo, 5%, and 10% granular dressings showing the percent survival (Panel A), mortality based on sex (Panel B, gray females and males black), MAP (Panel C), heart rate (Panel D), core temperature (Panel E), and rectal temperature (Panel F). The treatments are identified by placebo granules (■), 5% granules (○), and the 10% granules as (Δ). The time course of the experiment is shown in the shaded bar inset where (a) is the 5 minutes of manual compression, (b) is the observation/resuscitation phase.

A chitosan based dressing has been previously evaluated in a model of hepatic injury (Pusateri, AE et al. J. Trauma, 2003, 54, 177-82). This study utilized the injury model described by Holcomb (Holcomb, JB et al. J. Trauma, 1999) wherein a chitosan patch dressing applied to the wound resulted in an 87.5% survival rate at 60 minutes compared to a 38.4% rate using a gauze sponge. The dressings developed in our laboratories manifest a 100% survival, in all but one formulation, at 60 minutes post injury. However, utilizing the results reported by Pusateri the survival percentages are statistically insignificant.

Thermal stability studies

The efficacy of a hemostatic dressing is but one criterion important to successful development. The stability of the dressing and/or drug component is a critical factor affecting the ultimate viability of a candidate dressing for battlefield deployment. As part of the development process we have evaluated the thermal stability of 10% CP-305 loaded patches at 2 to 8°C, 25°C-60% relative humidity, and 40°C-60% relative humidity over 9 months (Figure 11). The thermal stability of CP-305 was also evaluated at temperatures up to 50°C under sealed container conditions (Figure 12). The drug in the patch formulations was stable for 2 months followed by a slow loss of active ingredient over the course of 7 months, 12 month stability data will be collected in March, 2008. The loss of 15% active at 40°C and 12% at 25°C and 2 to 8°C is believed to be associated with moisture accumulation within the packaging material (a polypropylene film) and patch over time. The degradation of the drug in sealed containers was significantly reduced thus suggesting that a moisture barrier packaging, which would be employed in the final dressing, will reduce the degradation of CP-305, as seen in the sealed vial experiments. The granule formulations will be evaluated for thermal stability; however, the high porosity of the granules is predicted to trap greater moisture. If moisture is the critical factor to stability then it will essential to package the dressing moisture resistant material to achieve a shelf life of 24 months.

**Figure 11**

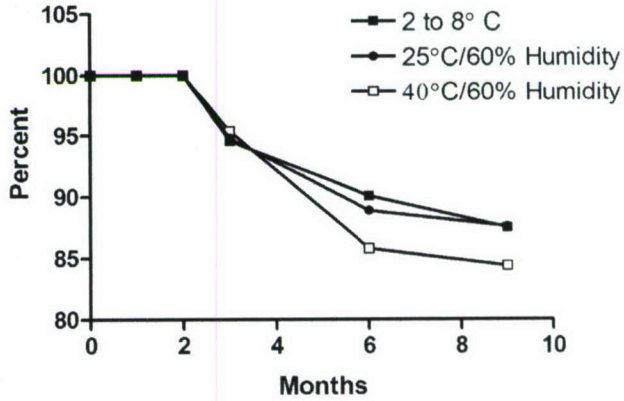
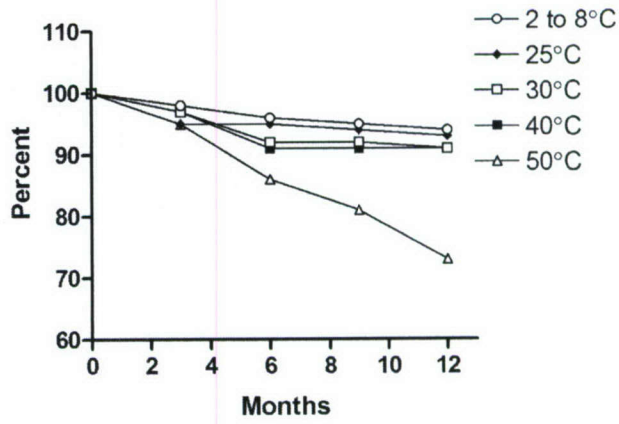



**Figure 12**




Mechanism of hemostatic action of CP-305

A second tract of the research effort was to develop novel hydrolysable vanilloid receptor 1 (VR-1) agonist for potential use as internal hemostatic agents. Prior to initiating a full scale synthetic effort to identify new drug candidates it was essential to validate the mechanism of action of CP-305. Our original mechanism of action focused on the pronounced vasoconstriction of microvascular beds in

response to CP-305 application. However, in the course of the rat model hemostatic studies it was observed that the blood in wound sites and dressing because very "hard" in comparison to vehicle controls. It was therefore hypothesized that the drug affected blood clotting as well as microvascular responses. From a mechanistic standpoint, studying mechanism in blood is less technically demanding than studying signaling pathways in microvascular beds. Thus, the elucidation of the hemostatic action of CP-305 was examined in blood and blood cell types.

Mechanistic studies began with whole blood and platelet rich plasma aggregation studies using rat, swine, and human samples. In phase I, aggregation studies were conducted on whole blood samples using increasing concentrations of CP-305. In the experiments the drug in ethanol (EtOH) or EtOH alone were evaluated at drug concentrations from 10nM to 100 μM wherein not affect on aggregation was observed. At 1 mM a small response was detected, however a final concentration of 10 mM was required to induce a measurable aggregation response, *i.e.* increase in impedance (Figure 13). The response occurred in 2 phases, an early but small change in impedance occurred within 5 minutes, followed by a plateau then a significant increase in impedance after approximately 20 minutes. Vehicle controls did not manifest a significant increase in impedance over the 40 minute time course. The high concentration and long time course was atypical of a normal aggregation response. These results were of concern because it suggested a non-specific effect of the drug on aggregation. It was determined that precipitation did occur after drug addition which may trigger platelet activation. However, studies using platelet rich plasma and increasing drug concentrations (10nM to 10 mM) failed in induce platelet aggregation thus suggesting an alternate mechanism of action.

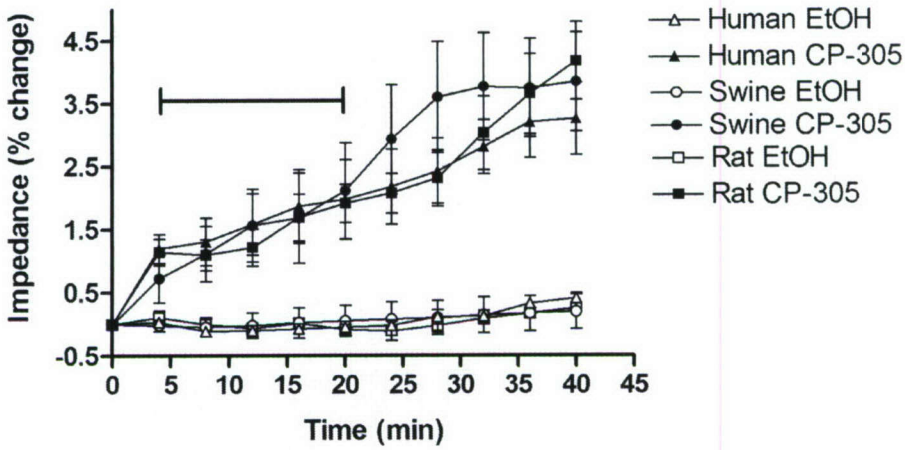



**Figure 13.** Whole blood aggregation studies on human (n = 6), swine (n = 6), and rat (n = 4) blood samples from different donors. CP-305 in EtOH (10μl) or EtOH (10μl) as added to the sample and the change in impedance was monitored for 40 minutes. An approximately 2 fold increase in impedance occurred in 4 minutes followed by a plateau phase (shown by the bar in the graph). A second aggregation phase occurred 15 to 20 minutes post drug addition.

The data from the aggregation studies suggested the mechanism of action was not related to platelet activation. To further restrict the potential site(s) of action, the presence of VR-1 in human and rat platelets was tested using PCR and RT-PCR. (the sequence of the swine VR-1 is unknown and therefore not studied). The PCR studies show that message for VR-1 is present in the rat and human platelets (Figure 14). However, an analysis of the message via RT-PCR indicates that the level of the

message, relative to the housekeeping gene GAPDH, is relatively low (Table 6). The low level of message in these platelets suggested that VR-1 agonist may act via a novel mechanism. This may explain the "induction" phase in the whole blood aggregation in that coagulation may need to be primed via another process. Two potential mechanisms based on thromboxane release and/or superoxide release from neutrophil activation was proposed.

**Table 6**

| | Cycle number | | |
|---|---|---|---|
| Species | GAPDH | VR-1 | *delta* |
| Human | 18.36 | 31.27 | 12.91 |
| Rat | 16.52 | 32.32 | 15.80 |

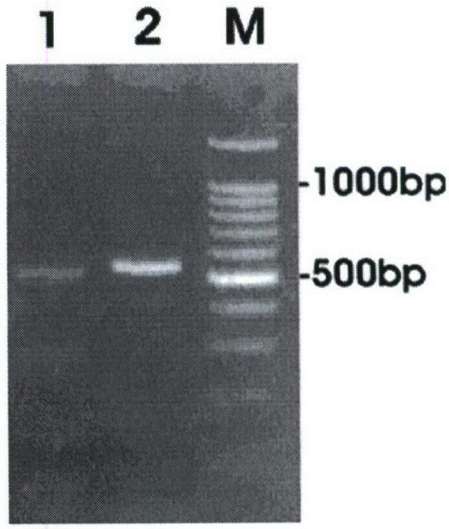



**Figure 14.** DNA fragments were amplified by PCR from rat and human platelets. PCR products were run in a 2% agarose/ TBE/ethidium bromide gels. The sizes of DNA fragments amplified in the PCR reactions are indicated as follows: lane 1 human 513bp, lane 2 rat 539bp. Lane M: DNA markers used to estimate size.

Thromboxane assay using whole blood

Platelet activation/aggregation is triggered by the interaction of ligands (thrombin, collagen, or ADP) with cognate receptors found on the surface of platelets. Receptor-ligand interactions trigger the release of thromboxane A2 (TXA2), which in turn activates TXA2 receptors on platelets. TXA2 receptor activation results in the release of Ca2+ stores via activation of phospholipase C. The increase in intracellular Ca2+ amplifies platelet aggregation and results in the release of TXA2 and ADP from activated platelets completing the positive feedback loop. It was proposed that CP-305 may affect this aggregation mechanism by an unknown mechanism. Specifically, platelet rich plasma was insensitive to the presence of drug thus removing a platelet based component in the early aggregation phase. These results lead to the hypothesis that a component in whole blood affected the release of TXA2 which acts downstream on platelet activation. Such a mechanism could account from the biphasic aggregation profiles observed in whole blood.

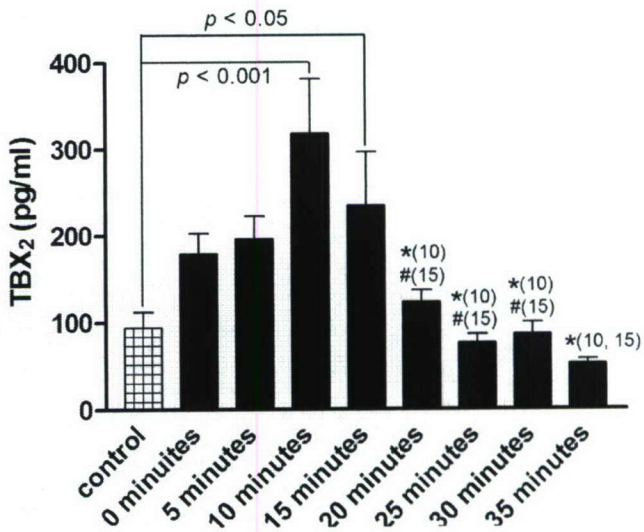



**Figure 15.** The effect of CP-305 on the TBX2 levels in whole blood as a function of time. The statistical significance is shown as *(10) is a $p = 0.001$ in comparison to the 10 minute time interval; #(15) is a $p = 0.05$ in comparison to the 15 minute time interval; and *(10,15) is a $p = 0.001$ in comparison to the 10 and 15 minute time interval.

TXA2 is inherently unstable and thus its stable metabolite TXB2 was used as a surrogate marker for TXA2. Whole blood from 6 human volunteers was treated with 10 mM CP-305 (10 µl in EtOH) then the samples were centrifuged at 0, 5,10,15,20, 25, 30, and 35 minutes and the plasma collected and flash frozen. In control experiments samples were immediately centrifuged after collection and plasma treated as before. The thromboxane

concentration in the plasma samples was quantified using TBX2 ELISA method (Cayman Chemical). Figure 15 shows the change in TBX2 as a function of time. The addition of CP-305 to whole blood results in a statistically significant spike in TBX2, relative to control samples, 10 and 15 minutes post addition. The concentration of TBX2 at 20 minutes is significantly lower than the peak but statistically insignificant relative to control samples. The rise in TBX2 levels correlates with the plateau phase in whole blood aggregation studies (Figure 13) suggesting that TBX2 initiates the second phase aggregation response. However, the initiating trigger for blood aggregation remains unclear.

Superoxide

Neutrophils with platelets attached have enhanced adhesion molecule expression and elaborate more superoxide than neutrophils not associated with platelets. Thus, the platelet-leukocyte aggregate fraction is indicative of the degree of platelet and leukocyte activation. Activated neutrophil-platelet interactions may be an initiator of aggregation in whole blood samples and thus constitute a mechanism of CP-305 action. To assess the role of superoxide, a marker of neutrophil activation, the release of superoxide from purified swine neutrophils was tested. The isolation of neutrophils is a sensitive procedure requiring large volumes of blood thus the swine blood was selected. Purified neutrophils in platelet poor plasma were treated with 20 mM CP-305 (10 µl EtOH) in glass luminometer tube containing luminol (1 mM). Samples were monitored as a function of time using a single tube luminometer (Berthold Detection Systems). Control samples consisted of 10 µl of EtOH and luminol only assays. Figure 16 shows that neither CP-305 nor EtOH caused a significant increase in superoxide levels; however, luminol alone caused a time dependent increase in luminance. The data suggest that a neutrophil activation is not occurring; however, we are cautious in the data interpretation because precipitated CP-305 may have interfered with the detection of luminescence.

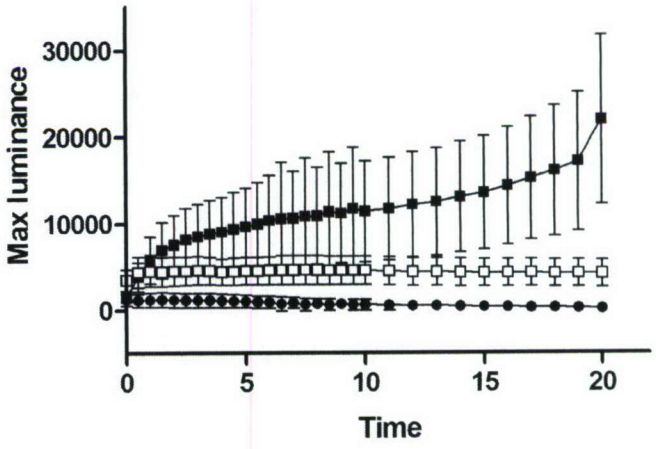


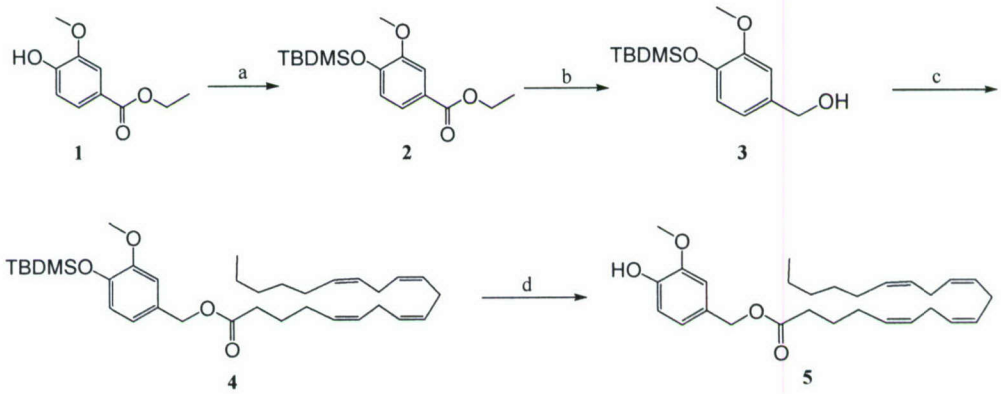

**Figure 16.** The effect of CP-305 on the activation status of swine neutrophils. The experiments tested the effects of CP-305 (●), EtOH (□), and luminol (■) on superoxide release as a function of time.

Synthesis of novel vanilloid based hemostatic drugs.

The identification of vanilloids as hemostatic agents promoted the investigation into enzymatic hydrolysable analogs with the intent of expanding the compounds beyond topical agents. The design of the analogs was based on a bioisosteric replacement of the amide in arvanil and capsaicin with ester functionality. We developed a synthetic methodology for the preparation of ester based vanilloids as shown in Scheme 1. The synthesis begins with the protection of the phenolic group in vanillyl ethylester (**1**) with TBDMS-Cl provided **2** in 96 percent yield. Reduction of the ester with LAH yielded **3** followed by ester formation using arachidonyl chloride. Subsequent deprotection of the phenolic group using TBAF in THF yielded the final product **5**. Optimization of the synthetic methodology was suspended until a defined mechanism of action for CP-305 is elucidated. This

decision was made because without a clear target it would be impossible to conduct *in vitro* screening of new drug candidates.

**Scheme 1**




a) TBDMSCl, imidazole, DCM, overnight; b) LAH, THF, reflux, overnight; c) archidonoyl chloride, pyridine, DCM, 12 hrs, rt; d) TBAF, THF, rt, 1 hr.

*Experimental*

All solvents were distilled from either calcium hydride or sodium metal prior to use. TLC chromatograph was conducted on Sorbent Technologies, Aluminum backed TLC plates with UV254, 200 um thickness. Column chromatograph was carried out on a Biotage Purification system, Model SP-1;Cartridges using 40 M and 12 M columns. Mass spectra were obtained on a Bruker Esquire – LC/MS , electro spray ionization (ESI) mode and NMR spectra were collected on either a Varian 500 MHz or a Bruker 300MHz NMR spectrometer.

*Synthesis of 4-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-benzoic acid ethyl ester* (**2**).

To a solution of the vanillyl ester (**1**) (1 eq, 51mmol) and imidazole (2 eq) in 250 ml of anhydrous DCM, 1 eq of TBDMSCl was added at room temperature and was stirred for 12 hours. After the completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. The oily residue was then re-dissolved in DCM, followed by washes with saturated solution of sodium bicarbonate, brine and water. The organic layer was separated and dried over sodium sulfate, filtered and dried under reduced pressure to yield oil that was further purified using column chromatography over silica gel using 10% ethyl acetate/ hexanes as solvent. Yield = 95.6%, as a clear oil, product $R_f$ = 0.58, 1H NMR, 500 MHz, $CDCl_3$, δ 7.59 (d, J=8.00 Hz, 1H), 7.55 (d, J=2.00 Hz, 1H), 6.87 (d, J=8.50 Hz, 1H), 4.35 (q, J=7.00 Hz, 2H), 3.86 (s, 3H), 1.38 (t, J=7.00 Hz, 3H), 1.00 (s, 9H), 0.18 (s, 6H); MS: m/z (ESI, pos.) = 333.2 ([M+23])

*Synthesis of [4-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-phenyl]-methanol* (**3**).

To a stirred solution of (**2**) in anhydrous THF, 2 eq of $LiAlH_4$ was added and the resulting suspension was stirred for 1 hr, followed by refluxing for 12 hrs. The resulting suspension was then treated with ice water followed by the addition of 0.1 N HCl. The organic layer was then separated and dried over sodium sulfate, filtered and the solvent was removed under pressure to yield an oil. The crude product was further purified using column chromatography with 10 % ethyl acetate/hexanes as solvent system. Yield = 11.0%, as a clear oil, product $R_f$ = 0.43, 1H NMR, 300 MHz, DMSO δ 6.95 (s, 1H), 6.76 (d,

J=.056 Hz, 2H),5.08 (t, J=5.74, 1H), 4.53 (d, J= 5.75 Hz, 2H), 3.75 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H), MS: m/z (ESI. pos.) = 291.0 ([M+23])

*Synthesis of Eicosa-5,8,11,14-tetraenoic acid 4-(tert-butyl-dimethyl-silanyloxy)-3-methoxy-benzyl ester* (**4**).
Compound 3 was dissolved in 15 ml of dry DCM under an inert atmosphere and cooled in an ice water bath. The arachidonyl chloride (1.2 eq) was dissolved in 10 ml of anhydrous DCM and was added drop wise to the reaction mixture. The reaction was then allowed to warm up to room temperature and stirred for 30 min Pyridine (1.2 eq was then added to the reaction mixture and the reaction was stirred for an additional 15 hrs. after the completion of the reaction as indicated by the TLC, the reaction was quenched with 10 % NaOH solution, followed by washes with brine and water. The organic layer was separated and the dried over sodium sulfate, filtered and the solvent removed under vacuum. The crude product was purified using column chromatography with 10 % ethyl acetate/hexanes as solvent system. Yield = 51.5%, as an oil, product $R_f$ = 5.34, 1H NMR, 300 MHz, $CDCl_3$, δ 6.84 (d, J=0.90 Hz, 1H), 6.81 (d, J=1.20 Hz, 2H), 5.43-5.29 (m, 8H), 5.03 (s, 2H), 3.80 (s, 3H), 2.85-2.77 (m, 6H), 2.36 (t, J=7.70 Hz, 2H), 2.14-2.02 (m, 4H), 1.77-1.67 (m, 2H), 1.38-1.26 (m, 6H), 0.99 (s,9H), 0.88 (t, J= 6.90 Hz, 3H), 0.15 (s, 6H); MS: m/z (ESI. pos.) = 577.5 ([M+23]).

*Synthesis of Eicosa-5,8,11,14-tetraenoic acid 4-hydroxy-3-methoxy-benzyl ester* (**5**)
To a solution of 4 in dry THF, 1 eq of TBAF was added ant the resulting mixture was stirred for an hour. After the completion of the reaction, the organic layer was washed with sodium bicarbonate solution which resulted in an emulsion. Attempts to break the emulsion with n-butanol and MTBE were not successful although limited phase separation occurred. A sample of the crude organic phase was then purified by preparative TLC using 15 % ethyl acetate/ hexanes as a solvent system to obtain a clear oil. Yield = 69%, $R_f$=0.69, 1H NMR, 300 MHz, δ 6.90 (s, 1H), 6.74 (d, J=2.4, 2H), 4.95 (s, 2H), 3.74 (s, 3H), 2.31 (t, J=7.20, 2H); MS: m/z (ESI.pos.) = 463.3 ([M+23]).

CONCLUSIONS: The principle objective of the research was to translate the results of rat hemostatic studies into the swine models of lethal groin injury and liver laceration. Granules and patch formulations containing CP-305 were evaluated in normothermic models. Additionally, the effect of coagulopathy on hemostasis was examined in the lethal groin injury model. Drug loaded granules and patches provided rapid hemostasis in the normothermic vascular injury model manifesting survival rates from 70 to 90%. The survival percentages of animals treated with the novel hemostatic dressings compared to a SD dressing (100% mortality) was highly significant. The ability of the CP-305 dressings to maintain wound closure in the absence of added hemostatic measures, *e.g.* external pressure bandage covering the wound, may be an important outcome of the studies. Specifically, the data suggests that the dressings can be applied, manually compressed for 5 minutes, and released allowing for more rapid application to multiple injury sites. Ultimately, external fixation would be applied in battlefield situations to prevent mechanical failure, thus the properties of the CP-305 dressing would be important in the initial phase of hemorrhage control. It will be important to evaluate the efficacy of existing dressings without external fixation. These studies will provide critical data for one on one comparisons of hemostatic efficacy that is not justified under the current experimental conditions.

The efficacy of CP-305 in affecting hemostasis was validated in the granule formulations. Specifically, drug loaded granules manifested a statistically significant increase in survival relative to the placebo control. The efficacy of granules was not affected by hypothermia induced coagulopathy

or the lack of external fixation. These data combined with the 100% survival rate in the liver laceration model are compelling evidence for the continued development of the CP-305 based dressings. However, there are additional characteristics of a hemostatic dressing that must be considered in the final evaluation. The following characteristics are set forth by Pusateri (Pusateri, AE et al. J. Trauma, 2006, 60, 674-82) are desired in an ideal hemostatic dressing: 1) the product should be ready to use with no mixing or pre-activation; 2) application of the dressing is simple; 3) the dressing should be lightweight and durable; 4) the dressing should be stable over a wide range of environmental conditions for long periods; 5) the product should be safe to use with minimal training requirements; and 6) per unit cost of the dressing is a critical determinate in fielded large numbers of dressings.

The knowledge and experience gained in the course of the research has lead us to conclude that the granule hemostatic dressing conforms to most if not all the aforementioned ideal characteristics. In our experiments 20 grams of the ready to use granule formulation, contained in a plastic vial, was simply poured into the wound site followed by manual pressure. The final product contained in a moisture resistant tear open package would be light weight (50 to 100 grams) and rapidly deployed. The mechanical stability of the granules was not systematically studied; however, the granules were not compromised in the pan coating process and were resistant to manual crushing. The thermal stability of CP-305 powder (7 percent loss at 40°C over 12 months) indicated that long term stability, *i.e.* 24 months, can be achieved with the proper protection from moisture accumulation. The active ingredient CP-305 is currently approved for topical application although the safety in an open wound remains to be determined. Residual powder in the granules from the manufacturing process was mildly irritating to a few individuals and must be considered. We believe this side effect can be overcome by defining the granular particle size and/or by the application of a rapidly dissolving granular coating. A cost analysis for manufacture has not been conducted; however, the bulk materials are inexpensive and the manufacture process employs standard pharmaceutical methodologies. As such we believe that the final produce will be highly competitive from a cost perspective.

The mechanism of action of CP-305 in hemostasis remains unclear; however, our data suggests that vascular constriction and coagulation are contributing to the efficacy of the drug. One consideration that we are now investigating is the possibility that a trace impurity in the bulk CP-305 is, in part, responsible for hemostatic activity. This line of investigation was prompted by the high CP-305 (mM) concentration required to affect coagulation. If in fact a 0.1 % or less impurity possess coagulation activity this would translate to 100 nM to 1 μM concentration at the current CP-305 concentrations used for aggregation studies. Activity of an impurity in the nM range would suggest a novel target that may be exploited for the development of higher efficacy hemostatic dressings.

SIGNIFICANCE: Our studies have provided the pre-clinical evidence of the efficacy of CP-305 loaded dressings in establishing hemostasis in the vascular injury and liver laceration swine models. The results validate a novel technology for preventing exsanguination due injuries sustained on the battlefield.

PATENT INFORMATION: A patent application is pending on the use of CP-305 and related compounds for hemorrhage control. U.S. Patent Application Serial No. 10/411,479 "Method and Kit for Controlling Bleeding" Filed: April 8, 2003. B.M. Moore II, D. D. Miller.

AWARD INFORMATION: MBJ Health Care Hero Award for Innovation (2005)

REFEREED PUBLICATION:

Three manuscripts are currently in preparation on the rat and swine work. One manuscript is planned on the formulation and manufacture of the patch and granule formulations.

BOOK CHAPTERS, SUBMISSIONS, ABSTRACTS AND OTHER PUBLICATIONS

B. M. Moore II, G. Dabas, H. Bhattacharjee, S. Bavadekar, S. Gurley, X. Zhang, R.K. Nallamothu, H. Desu, D. Murali, G. Wood. Development of CP-305 as a Novel Hemostatic Agent. 2005 ATACCC Conference, St. Petersberg, FL, 2005.